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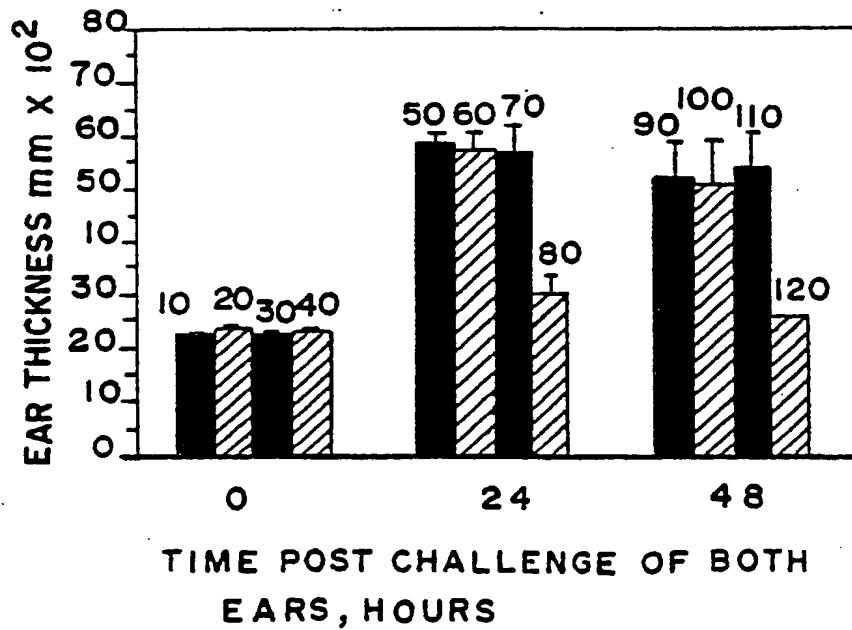
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(54) Title: TOPICAL NIFEDIPIINE FOR CUTANEOUS, OCULAR, MUCOSAL HYPERSENSITIVITY, INFLAMMATORY AND HYPERPROLIFERATIVE CONDITIONS



(57) Abstract

A method and composition for the topical treatment of cutaneous, mucosal or ocular hypersensitivity reactions, inflammatory, or epithelial hyperproliferative states, including those associated with scarring. The composition, to be applied to an affected area of the skin, eye, or mucosal membrane, consists of a therapeutic amount of nifedipine or related compound thereof, which has been incorporated into a vehicle suitable for topical administration.

* See back of page

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TOPICAL NIFEDIPIINE FOR CUTANEOUS, OCULAR, MUCOSAL
HYPERSENSITIVITY, INFLAMMATORY AND HYPERPROLIFERATIVE CONDITIONS

5

BACKGROUND OF THE INVENTION

Cutaneous, ocular, and mucosal inflammation, the development of changes in vascular tone and permeability and the associated infiltration of the skin, ocular, or mucosal tissues by leukocytes in response to endogenous or exogenous stimuli, probably evolved as a defense mechanism against infectious agents. However, even in healthy adults, cutaneous, ocular, and mucosal hypersensitivity can occur in response to certain plant resins, such as those of poison ivy, and other commonly encountered agents in the environment. In individuals sensitized to these agents, a severe contact reaction can result upon exposure with significant associated morbidity. Inflammation also occurs in association with reactions to physical agents such as sunlight and in association with thermal, electrical or chemical burns. Severe or repeated inflammatory reactions can be followed by significant chronic changes, such as scarring of affected tissues. In some anatomical sites, such as the eye, these chronic changes can have serious long term consequences, including diminished vision or actual blindness.

It is now widely recognized that much cutaneous, ocular, and mucosal inflammation is pathological in nature. For example, in atopic dermatitis and eczema in general, leukocyte (particularly mononuclear cells, lymphocytes, neutrophils, and eosinophils) infiltration into the skin is a general phenomenon and is important in the pathogenesis of these diseases. Similarly, psoriasis, a common cutaneous disease associated with a

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hyperproliferating epidermis, also has an inflammatory component. It is now believed that cells found in the normal and abnormal skin, eye, or mucosal membranes secrete cytokines which are important in recruiting 5 inflammatory leukocytes into these sites and in inducing chronic changes such as scarring.

In addition to contact dermatitis, atopic dermatitis and eczema, other conditions involving pathogenic cutaneous, ocular, and mucosal inflammation 10 include, but are not limited to psoriasis, acne vulgaris, arthropod bite reactions pyoderma gangrenosa, lichen planus, cutaneous lupus erythematosus, scleroderma, mycosis fungoides, burns, and drug eruptions. These 15 conditions may result in the following one or more symptoms or signs: itching, swelling, reddening, blisters, crusting, pain, scaling, cracking, scarring or oozing of fluid involving the skin, eye or mucosal membranes.

The potential therapeutic benefits of controlling 20 pathological cutaneous, ocular, or mucosal hypersensitivity, inflammation, hyperproliferation, and scarring, has led to a search for therapeutic agents which are both safe and effective. Several substances 25 are known to have the capability of inhibiting cutaneous leukocyte responses or hyperproliferative responses. Corticosteroids when administered systemically are effective in this regard, but are associated with significant and potentially dangerous side affects. Topically applied corticosteroids have some efficacy in 30 treating these conditions, but are only partially effective in many instances, and have their own significant side effects. Cyclosporine A is also partially efficacious systemically, but of little or no utility when applied topically. Cyclosporine A is also 35 associated with the real potential of serious toxicity to

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several major organ systems. Other agents with partial utility for treating some of the above conditions include, psoralen plus ultraviolet A (PUVA), dapsone and anti-malarials, but the risk to benefit ratios for these 5 agents is unfavorable for most of these conditions.

There is a significant and very long-standing need to identify agents which can be applied topically to prevent or suppress (i.e. "treat") cutaneous, ocular, or mucosal hypersensitivity reactions, inflammation, 10 hyperproliferation, or scarring, and which have favorable benefit to risk ratios. Optimally such agents should primarily act locally, and systemic absorption should not result in blood levels high enough to cause significant systemic toxicity.

15 It is an object of the present invention to present a method for the topical treatment of reactions of cutaneous, mucosal, or ocular hypersensitivity.

20 It is another object of the present invention to present a method for the topical treatment of cutaneous, mucosal, or ocular inflammation.

It is yet another object of the present invention to present a method for the topical treatment of cutaneous, mucosal, or ocular epithelial hyperproliferation.

25 It is yet another object of the present invention to present a method for the topical treatment of cutaneous, mucosal, or ocular scarring.

It is further an object of this invention to 30 present a composition for the topical treatment of cutaneous or mucosal hypersensitivity reactions, inflammation, hyperproliferation, or scarring, containing a therapeutic amount of a calcium channel blocker such as nifedipine or related compounds such as verapamil, diltiazem, isradipine, McN-6186, bepridil, niludipine 35 perhexiline, nicardipine, flunarizine, nilvadipine,

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nisoldipine, nitrendipine, felodipine, cinnarazine, and nimodipine.

It is more specifically an object of this invention to present a composition for the topical treatment of cutaneous, ocular or mucosal hypersensitivity reactions, inflammation, hyperproliferation or scarring which consists of dissolving or suspending a calcium channel blocker selected from a member of the group consisting of 10 nifedipine, verapamil, diltiazem, isradipine, McN-6186, bepridil, niludipine, perhexiline, nicardipine, flunarizine, nilvadipine, nisoldipine, nitrendipine, felodipine, cinnarazine, and nimodipine, in an appropriate preparation for topical administration.

It is further an object of this invention to present a method and composition for the topical treatment of cutaneous, ocular or mucosal hypersensitivity reactions, inflammation, hyperproliferation, or scarring in a fashion that limits 20 significant systemic effects.

BRIEF SUMMARY OF THE INVENTION

The subject invention concerns novel topical compositions and method for inhibition of cutaneous, ocular or mucosal hypersensitivity reactions, 25 inflammation, hyperproliferation, or scarring. The preferred composition described herein comprises a calcium channel blocker, such as nifedipine, in vehicles suitable for topical application and cutaneous, ocular or mucosal absorption. In tests conducted in accordance with 30 the present invention, these compositions have been shown to be effective when applied topically in inhibiting cutaneous contact hypersensitivity reactions at the site of application, but at doses that do not inhibit this response at a distant site. This latter point is

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important since it shows that systemic absorption is not important for this effect.

In accordance with the present invention it has been discovered that the properties of nifedipine and other related calcium channel blocker drugs, make them useful as topical agents in treating contact dermatitis, atopic dermatitis, eczematous dermatitis, lichen planus, psoriasis and cutaneous lupus erythematosus, scleroderma, inflammatory acne, arthropod bit reactions, conjunctivitis, iritis keratoconjunctivitis, vaginitis, photosensitivity conditions including sunburn, chemical burns and thermal burns. The novel method may also be useful in reducing the infiltration of skin by malignant leukocytes in diseases such as mycosis fungoides.

In its broadest overall aspect the composition simply consists of a calcium channel blocker drug of the type described above, dissolved in a suitable carrier for topical administration. The method of treatment is to apply the composition onto the affected area of the skin, eye, or mucosal membrane.

BRIEF DESCRIPTION OF THE DRAWINGS

The sole figure is a graph which shows the effects of topical nifedipine on cutaneous hypersensitivity reactions (inflammation). The x axis represents time points 0, 24 and 48 hours after challenging both ears of mice with oxazolone and the y axis is measurement of ear thickness in $\text{mm} \times 10^{-2}$.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention is based on the discovery that cutaneous, ocular or mucosal hypersensitivity reactions, inflammation, epithelial hyperproliferation, or scarring, can be treated by topical formulations of the calcium channel blocker nifedipine and its related compound. Moreover, this effect can be directed to the

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site of application and immediate surrounding area without a significant similar systemic effect.

The conditions that the subject invention is therapeutically beneficial in treating include cutaneous hypersensitivity/inflammatory conditions such as contact dermatitis, atopic dermatitis, eczematous dermatitis, 5 lichen planus, lupus erythematosus, scleroderma, inflammatory acne, arthropod bite reactions, burns, and photosensitivity conditions, including sunburn; cutaneous 10 epidermal hyperproliferative conditions such as psoriasis and ichthyosis; and mucosal hypersensitivity/inflammatory conditions such as lichen planus, aphthous ulcers, vaginitis, proctitis, conjunctivitis, iritis and keratoconjunctivitis. Additionally, longstanding 15 inflammation can result in scar tissue formation in and around the affected site and suppression of such inflammation can prevent or lessen scar formation.

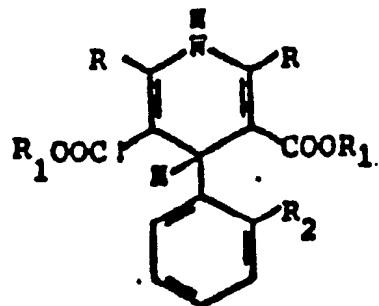
The subject invention pertains not only to nifedipine, a calcium channel blocker drug, but also to 20 derivatives and other related compounds which have similar biologic activity with respect to the control of inflammation, function, migration, and proliferation of cutaneous and mucosal cells. Other such related compounds may include, but are not limited to other 25 calcium channel blockers such as verapamil, diltiazem, isradipine, McN-6186, bepridil, niludipine, perhexiline, nicardipine, flunarizine, nilvadipine, nisoldipine, nitrendipine, felodipine, cinnarazine, nimodipine, and analogues and derivatives thereof.

30 Nifedipine and the above related compounds are presently used for controlling anginal attacks and hypertension. Calcium blocker drugs such as those listed above inhibit the transmembrane influx of calcium ions into many cell types including cardiac muscle, smooth muscle, leukocytes, and epithelial cells. Recent in 35

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vitro studies have also shown nifedipine to be effective in suppressing tumor necrosis factor induced adherence of neutrophils, a type of leukocyte, to human umbilical vein endothelial cells. Since nifedipine has been used in the 5 treatment of angina and hypertension, toxicity information is readily available. The information indicates that nifedipine has not been shown to be either carcinogenic or mutagenic or to have serious adverse reactions. By applying these agents topically, 10 therapeutic local concentrations are attainable without the associated systemic side effects.

Nifedipine that is used in the present invention can be generally presented by the formula:



wherein

15 R = a hydrogen or alkyl of 1 to 3 carbon atoms,
 R_1 = an alkyl of 1 to 4 carbon atoms, and
 R_2 = a hydrogen, halogen, or 1 or 2 lower alkyl, lower
 alkoxy, nitro, lower acylamino, lower alkylamino or amino
 moieties

20 Furthermore, the nifedipine of the subject
 invention and the other related compounds showing similar
 biologic activity can be modified in order to enhance
 their usefulness as pharmaceutical compositions. For
 example, it is well known in the art that various
 25 modifications, such as alteration of charge, can alter
 water and lipid solubility and thus alter the potential
 for percutaneous absorption. The vehicle can be
 similarly modified to enhance cutaneous absorption,
 enhance the reservoir effect and minimize irritancy of

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of the composition. Additionally, the topical formulation can be occluded to further enhance absorption. Preservatives, stabilizers, emulsifiers, emulsion stabilizers, antioxidants, chelating agents, 5 solvents, thickening agents, emollients, and humectants may be necessary or useful as part of the topical formulation. (Arndt, K.A., P.V. Mendenhall [1987] The Pharmacology of Topical Therapy. In Dermatology in General Medicine. T.B. Fitzpatrick, A.Z. Eisen, K. Wolff, 10 I.M. Freedberg and K.F. Austen, eds., 3d ed., McGraw Hill, Inc., New York, pp. 2532-2540). In addition, natural or artificial flavorings or sweeteners may be added to enhance the taste of topical preparations applied for local effect to mucosal surfaces. Inert dyes 15 or colors may be added, particularly in the case of preparations designed for application to oral mucosal surfaces.

Suitable vehicles or carriers for topical application may contain a daily dose of between 0.1 20 milligrams and 120 grams of between 0.001% to 100% (all percentages are by weight) of the calcium channel blocker nifedipine or a related compound, and may be prepared by conventional techniques to be in conventional forms such as lotions, suspension, ointments, creams, gels, 25 tinctures, suppositories, elixirs, solution, aerosols, sprays, powders, pastes or slow release polymers for topical application; or mouth rinses or rectal or vaginal suppositories for local/topical application to these respective mucosal surfaces. Suitable pharmaceutical 30 diluents, solvents or carriers include, water, alcohols, sterols, propylene glycol, glycerin, polyethylene glycol, diisopropyl adipate, 1,2,6-hexanetriol, isopropyl myristate, propylene carbonate, natural and/or synthetic or hardened oils and waxes, kaolin, talc, titanium 35 dioxide, as well as suitable solubilizers or emulsifying

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laureth sulfate, sodium lauryl sulfate, sorbitan esters, stearic acid, cetyl alcohol, cetearyl alcohol, or stearyl alcohol. Stabilizers such as benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, chlorocresol, 5 citric acid, edetate disodium, parabens, sodium bisulfite may be added. Thickening agents such as petrolatum beeswax, xanthan gum, or polyethylene, plus humectants such as sorbitol solution may also be added. Similarly emollients such as mineral oil, lanolin and its 10 derivatives, or squalene can be included as part of the topical formulation. Natural or artificial sweeteners including glucose, fructose, sucrose, aspartase, and saccharin may be added to enhance the palatability of preparations applied to mucosal surfaces. Similarly 15 flavorings such as peppermint oil may be added, Inert dyes, such as yellow dye number 6, may be added, particularly in the case of preparations designed for topical application to oral mucosal surfaces.

One important composition of the vehicle for the 20 subject invention is comprised of about 0.51% by weight of nifedipine dissolved in a vehicle consisting of about; 38% ethanol, 9.8% water, 0.8% sodium lauryl sulfate, 3.2% isopropyl alcohol, 30% propylene glycol, 1.03% glycerin, 0.026% peppermint oil, 0.026% saccharin, and 25 16.6% polyethylene glycol 400 (PEG 400). The nifedipine used is obtained from Pfizer in capsule form under the trade name Procardia and the liquid capsule contents were used for the experiments.

The sole drawing demonstrates the therapeutic 30 effect of 20 microliters of the above nifedipine preparation on the expression of contact sensitivity reactions in the right ears of mice. Mice were sensitized to 3% oxazolone (4-ethoxymethylene-2-phenyl-oxazol-5-one) in 4:1 acetone/olive oil, by applying 50 35 microliters to the shaved abdomen and 5 microliters to

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microliters to the shaved abdomen an 5 microliters to each hind footpad of each mouse, seven days earlier. On the day of treatment each side of both ears of the mice were challenged with 10 microliters of 0.5% oxazolone in 5 4:1 acetone/olive oil (i.e. 20 microliters per ear). One hour after challenge 10 microliters of the nifedipine or control preparation was applied to each side of a given ear (i.e. 20 microliters per ear). Each thicknesses of the mice were measured just before challenging with 10 oxazolone, bars 10, 20, 30 and 40. Of those mice given the nifedipine preparation only the right ears were treated, bars 80 and 120. The nifedipine preparation reduced the oxazolone induced inflammation (i.e. the contact sensitivity reaction to oxazolone) significantly 15 in the right ears of treated mice at 24 hours, bar 80 and at 48 hours, bar 120, after challenge with oxazolone as compared to the right ears of mice treated with 20 microliters of the vehicle preparation without nifedipine, bars 60 and 100. Similarly, the left ears of 20 the mice treated on the right ear with nifedipine showed no decrease in swelling, bars 70 and 110; ear thickness measurements of these ears were the same as those of ears treated with the vehicle preparation without nifedipine, bars 60 and 100, or of those of the left ears of the mice 25 treated on the right ears with vehicle lacking nifedipine, bars 50 an 90. The occurrence of undiminished swelling (increase in ear thickness) in the left ears of those mice treated with nifedipine topically on the right ear shows that the effect of topical 30 nifedipine is a local, rather than a systemic effect. Additionally, another vehicle preparation (not containing the active ingredient, nifedipine) has been shown to be ineffective in suppressing the ear swelling response. This vehicle was composed of about 1.86% water, 1.06% 35 glycerin, 0.026% peppermint oil, 0.026: saccharin, 17%

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propylene glycol. The lack of suppression of ears swelling by two complex vehicles (lacking the active ingredient nifedipine) is evidence that the calcium channel blocker nifedipine is necessary for the effect.

5 Topical preparations of nifedipine and other related compounds may be used in combination with other active compounds in order to enhance the topical preparation's anti-proliferative, anti-inflammatory, anti-hypersensitivity, or anti-scarring properties, or to
10 achieve additional therapeutic effects such as relief of pain or itching. For example, topical nifedipine preparations may be combined with topical corticosteroids, anti-fungal agents or anti-bacterial agents. For example, in the case of acne, a traditional
15 acne drug; such as erythromycin, clindamycin, benzoyl peroxide or a retinoid could be included as part of the preparation. Another example would be the addition to the preparation of an antifungal drug, such as clotrimazole, for the treatment of dermatophyte or
20 candida infection.

In practice a therapeutic amount of a nifedipine preparation is applied directly to the inflamed area of the skin, eye, or mucosal membrane and in a short period of time the inflammation is decreased.

25 It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and
30 purview of this application and the scope of the appended claims.

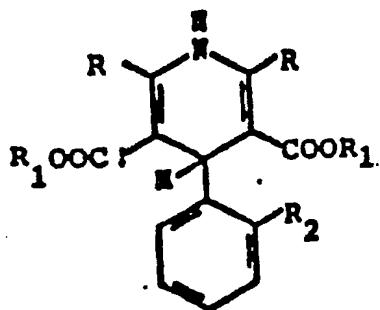
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CLAIMS

1 1. A method for locally treating cutaneous
2 hypersensitivity reactions, the method comprising
3 applying a therapeutically effective amount of a calcium
4 channel blocker to an affected area of the skin.

1 2. The method as set forth in claim 1 wherein the
2 calcium channel blocker applied is selected from a member
3 of a group consisting of: nifedipine, verapamil,
4 diltiazam, isradipine, McN-6186, bepridil, niludipine,
5 perhexiline, nicardipine, flunarizine, nilvadipine,
6 nisoldipine, nitrendipine, felodipine, cinnarazine,
7 nimodipine, and analogues and derivatives thereof.

1 3. The method as set forth in claim 1 wherein the
2 calcium channel blocker applied is nifedipine, said
3 nifedipine having the structure:



4 wherein
5 R = a hydrogen or alkyl of 1 to 3 carbon atoms,
6 R₁ = an alkyl of 1 to 4 carbon atoms, and
7 R₂ = a hydrogen, halogen, or 1 or 2 lower alkyl, lower
8 alkoxy, nitro, lower acylamino, lower alkyamino or amino
9 moieties.

4. The method as set forth in claim 1 wherein a daily dose between 0.1 milligrams and 120 grams of a

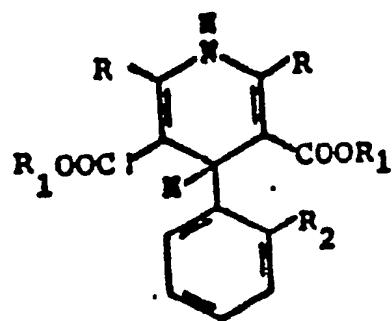
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3 preparation of topical nifedipine containing between
4 0.001% and 100% by weight of nifedipine is applied to the
5 affected area of the skin.

1 5. A method for the treatment of a cutaneous or
2 mucosal diseases involving hypersensitivity,
3 inflammation, scarring or epithelial hyperproliferation
4 selected from a member of a group consisting of: contact
5 dermatitis, acne vulgaris, lichen planus, pyoderma
6 gangrenosa, cutaneous lupus erythematosus, scleroderma,
7 mycosis fungoides, psoriasis, ichthyosis, burns, aphthous
8 ulcer, vaginitis, and proctitis, comprising applying a
9 therapeutically effective amount of a calcium channel
10 blocker to an affected area.

1 6. The method as set forth in claim 5 wherein a
2 calcium channel blocker applied is selected from a member
3 of a group consisting of nifedipine, verapamil,
4 diltiazam, isradipine, McN-6186, bepridil, niludipine,
5 perhexiline, nicardipine, flunarizine, nilvadipine,
6 nisoldipine, nitrendipine, felodipine, cinnarazine,
7 nimodipine, and analogues and derivatives thereof.

1 7. The method as set forth in claim 5 wherein the
2 calcium channel blocker applied is nifedipine, said
3 nifedipine having the structure:



4 wherein

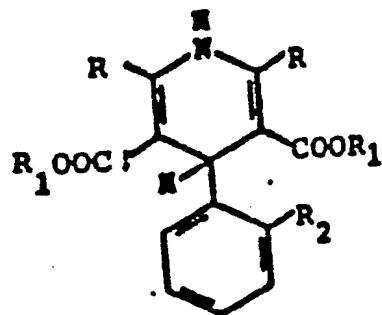
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5 R = a hydrogen or alkyl of 1 to 3 carbon atoms,
 6 R₁ = an alkyl of 1 to 4 carbon atoms, and
 7 R₂ = a hydrogen, halogen, or 1 or 2 lower alkyl, lower
 8 alkoxy, nitro, lower acylamino, lower alkyamino or amino
 9 moieties.

1 8. A method for the treatment of ocular
 2 inflammation comprising applying a therapeutically
 3 effective amount of a calcium channel blocker to an
 4 affected area of the eye.

1 9. The method set forth in claim 8 wherein a
 2 calcium channel blocker applied is selected from a member
 3 of a group consisting of: nifedipine, verapamil,
 4 diltiazam, isradipine, McN-6186, bepridil, niludipine,
 5 perhexiline, nicardipine, flunarizine, nilvadipine,
 6 nisoldipine, nitrendipine, felodipine, cinnarazine,
 7 nimodipine, and analogues and derivatives thereof.

1 10. The method as set forth in claim 8 wherein
 2 the calcium channel blocker applied is nifedipine, said
 3 nifedipine having the structure:



4 wherein
 5 R = a hydrogen or alkyl of 1 to 3 carbon atoms,
 6 R₁ = an alkyl of 1 to 4 carbon atoms, and

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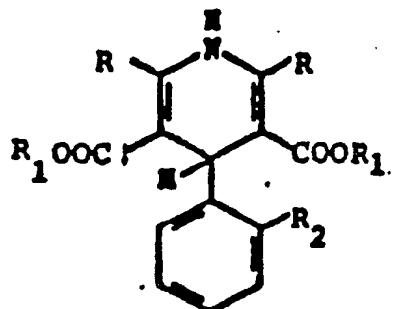
7 R_2 = a hydrogen, halogen, or 1 or 2 lower alkyl, lower
8 alkoxy, nitro, lower acylamino, lower alkyamino or amino
9 moieties.

1 11. The method as set forth in claim 8 wherein a
2 daily dose between 0.1 milligrams and 2 grams of a
3 preparation of topical nifedipine containing between
4 0.001% and 100% by weight of nifedipine is applied to the
5 eye.

1 12. A method for the prevention or reduction of
2 the formation of scar tissue in and around the eye,
3 comprising applying a therapeutically effective amount of
4 a calcium channel blocker to an affected area in or
5 around the eye.

1 13. The method as set forth in claim 12 wherein a
2 calcium channel blocker applied is selected from a member
3 of a group consisting of: nifedipine, verapamil,
4 diltiazam, isradipine, McN-6186, bepridil, niludipine,
5 perhexiline, nicardipine, flunarizine, nilvadipine,
6 nisoldipine, nitrendipine, felodipine, cinnarazine,
7 nimodipine, and analogues and derivatives thereof.

1 14. The method as set forth in claim 12 wherein
2 the calcium channel blocker applied is nifedipine, said
3 nifedipine having the structure:



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4 wherein

5 R = a hydrogen or alkyl of 1 to 3 carbon atoms,
6 R₁ = an alkyl of 1 to 4 carbon atoms, and
7 R₂ = a hydrogen, halogen, or 1 or 2 lower alkyl, lower
8 alkoxy, nitro, lower acylamino, lower alkyamino or amino
9 moieties.

1 15. A composition for the treatment of cutaneous,
2 ocular, or mucosal hypersensitivity reactions,
3 inflammation or cutaneous, mucosal or ocular
4 hyperproliferation, or the prevention or reduction of
5 associated scar tissue including that in and around the
6 eye, comprising of at least 0.001% by weight nifedipine
7 incorporated into a suitable vehicle for topical
8 application directly onto an affected area.

1 16. A composition as set forth in claim 15
2 wherein the calcium channel blocker to be incorporated
3 into a suitable vehicle for topical application is
4 selected from a member of a group consisting of:
5 nifedipine, verapamil, diltiazam, isradipine, McN-6186,
6 bepridil, niludipine, perhexiline, nicardipine,
7 flunarizine, nilvadipine, nisoldipine, nitrendipine,
8 felodipine, cinnarazine, nimodipine, and analogues and
9 derivatives thereof.

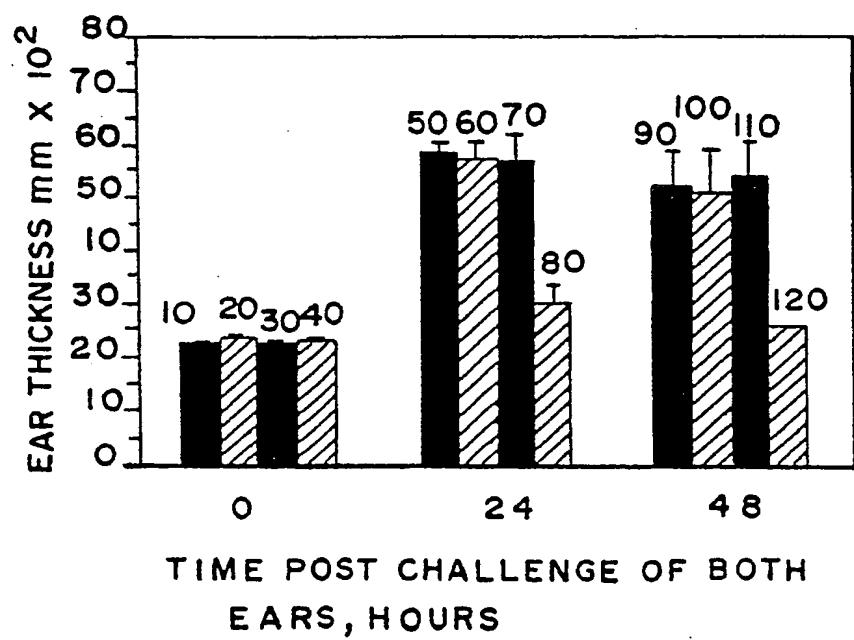
1 17. The composition as set forth in claim 15
2 wherein the composition further comprises the
3 incorporation of additional components which inhibit
4 cutaneous leukocyte accumulation selected from a member
5 of a group consisting of corticosteroids; other calcium
6 channel blockers such as verapamil, diltiazam,
7 isradipine, McN-6186, bepridil, niludipine, perhexiline,
8 nicardipine, flunarizine, nilvadipine, nisoldipine,
9 nitrendipine, felodipine, cinnarazine, nimodipine; and

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10 serotonin antagonists which include reserpine,
11 ketanserin, cyproheptadine, spiperone, methysergide, LY
12 53857, ritanserin, ICI 169-369, risperidone, pipamperone,
13 trazodone, cinanserin, mianserin, and LY 281067.

1 18. The composition as set forth in claim 15
2 wherein said composition further comprises the
3 incorporation of additional components which are active
4 against fungal infection selected from a member of a
5 group consisting of ketoconazole, itraconazole,
6 clotrimazole, oxiconazole, sulconazole, econazole, other
7 imidazoles, naftifine, ciclopirox olamine and nystatin.

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**SUBSTITUTE SHEET**

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/04632

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61F 2/00

U.S. CL. 424/427

II. FIELDS SEARCHED

Minimum Documentation Searched ⁷

Classification System	Classification Symbols
U.S.	424/430, 436, 422, 427, 434, 449, 443, 445, 448 514/914, 887

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are included in the Fields Searched ⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	US, A, 4,637,930 (KONNO ET AL) 20 JANUARY 1987; See entire document.	1-18
A	US, A, 4,766,213 (JURASZYK ET AL) 23 AUGUST 1988; See column 3, lines 12-20.	1-18

* Special categories of cited documents: ¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

28 SEPTEMBER 1990

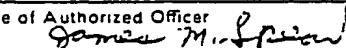
Date of Mailing of the International Search Report

04 JAN 1991

International Searching Authority

ISA/US

Signature of Authorized Officer


James M. Spear

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